DR. VIVEK R PATEL (Orcid ID : 0000-0001-6013-6960)

Article type : Original Article

A RANDOMIZED CLINICAL TRIAL ON THE EFFICACY OF 5% FLUOROCALCIUM PHOSPHOSILICATE CONTAINING NOVEL BIOACTIVE GLASS TOOTHPASTE

Vivek Rajiv Patel, MDS [1], Leena Shettar, MDS [1], Srinath Thakur, MDS FDSRCPS [1]

[1] Department of Periodontology and Implantology, Sri Dharmasthala Manjunatheshwara College of Dental Sciences and Hospital, Dharwad, Karnataka, India

CORRESPONDENCE ADDRESS: Dr. Vivek. R. Patel, Department of Periodontology and Implantology, SDM College of Dental Sciences and Hospital, Dharwad, Karnataka 580009, India. Phone no.: 9428611967. E-mail: vivek2611@yahoo.co.in

Conflicts of Interest: None of the authors have any conflicts of interest.

Source of Funding: The materials for the study were supplied by Group Pharmaceutical Limited, Rajaji Nagar, Bengaluru, Karnataka, India.

Acknowledgements:

The authors of this study would like to thank Dr David Gillam for his scholarly advice with which this manuscript was conceptualized and Dr. D.N Kamala for providing with the samples of toothpaste and toothbrush for the study.

Abstract:

Background and Aim: Dentin hypersensitivity (DH) is a common and harrowing dental condition. A Novel Biomin-F technology that contains 5% Fluorocalcium phosphosilicate bioactive glass has been introduced. It forms Fluorapatite which is more stable towards acid erosion. There is a lack of literature with the utility of this toothpaste in treating DH. Therefore, the authors of this randomized clinical trial have aimed to compare and evaluate the efficacy of 5% Fluorocalcium Phosphosilicate with an 8% Arginine and Calcium carbonate and Placebo toothpaste.

Methods: A total of 75 patients clinically diagnosed with DH were randomly divided into Group A: 5% Fluorocalcium Phosphosilicate, Group B: 8% Arginine and Calcium carbonate, and Group C: Placebo. The DH was evaluated by tactile and evaporative stimuli and a visual analog scale (VAS) was used for evaporative stimuli at Pre-baseline, Baseline (15 days) and Post-baseline (1 month).

Results: The results showed symptoms of DH were reduced in all three groups. However, Group A showed a better reduction of DH than the other two groups.

Conclusion: The toothpaste containing 5% Fluoro Calcium Phosphosilicate was reported to be more efficacious than the other two toothpastes in managing DH.

Practical Implications: This novel development opens up a unique opportunity in the prevention and management of DH and may also be beneficial in preventing acid erosion of

the tooth surface and in the maintenance of oral hygiene by reducing the effects of plaque accumulation and gingival inflammation.

Keywords: Dentin sensitivity, Calcium carbonate, Fluorapatite, Arginine, Toothpastes, Visual analog scale, Apatites.

Introduction:

Dentin Hypersensitivity (DH) is an enigma which is frequently encountered but is not fully understood.[1] It is exemplified by a short, sharp pain arising from exposed dentin in response to a stimuli; typically thermal, evaporative, tactile, osmotic or chemical and which cannot be ascribed to any other form of dental defect or pathology.[2] Based on the procurable disquisition the distribution data primarily neglects the number of teeth affected and the range of pain scores experienced per individual. This absence of information makes it difficult to make an accurate judgement of how DH impacts on the quality of life of sufferers.[1]Essentially the treatment of DH can be either by the interruption of pulp nerve response or through tubule occlusion. Tubule occlusion has been demonstrated to occur by clinical observation and through *in vitro* and *in situ* studies. Unfortunately, the resistance of the deposited material to etiological agents, notably abrasion and/or erosion, is rarely tested, and certainly some deposits on the exposed dentin surface are very acid labile.[1,3] Currently the epitome in the tubular occlusion approach for the treatment of DH includes formulations such as Novamin® and Pro-Argin®. The Novamin formulation formed a hydroxycarbonate like apatite (HCA) on the dentin surface and occluded the tubules.[4] However, an *in vitro* study[5] comparing HCA to Fluorapatite (FAP) crystals in a tris buffer solution for acid erosion and reported that FAP was more acid resistant. Based on the results of this study, the Biomin-F formulation was conceptualized which contains 5% Fluorocalcium phosphosilicate as its active ingredient that subsequently forms FAP crystals in contact with saliva rapidly

occluding the tubules. This recently introduced formulation has not been extensively researched by clinicians and researchers. Currently there appears to be limited *in vivo* studies[6] on Biomin-F, although several *in vitro* studies[7,8] have published. Therefore as a result of the limited data available that would support the efficacy of this formulation it was considered appropriate to conduct a study to evaluate the efficacy of Biomin-F for the treatment of DH.

There are numerous products that have been demonstrated to be effective for the treatment of DH, for example, Pro-Argin® desensitizing toothpastes based on its tubular occluding properties.[9-13] It was therefore considered appropriate to compare Biomin-F® to the Pro-Argin® formulation in the management of DH. The primary objective was to evaluate the reduction of DH whereas the secondary objective was to evaluate changes with PI and GI. The null hypothesis of the study was that there was no statistically significant difference in the efficacy of the Biomin-F® and Pro-Argin® toothpastes, whereas the alternate hypothesis was that Biomin-F® toothpaste was more efficacious than Pro-Argin® comparator in managing DH.

Materials and methods:

Study design:

The study was a randomized, triple blinded, two treatment, parallel arm clinical trial with an allocation ratio of 1:1. The study protocol was approved by the Institutional Review Board at the SDM College of Dental Sciences and Hospital, Rajiv Gandhi University of Health Sciences (IRB.No. 2016/P/PERIO/64) and was registered with the Clinical trials registry of India (CTRI/2018/05/014136). Each subject provided informed consent after a thorough explanation of the nature, risks, and benefits of the clinical investigation.

Study Population:

Patients reporting to the Department of Periodontology and Oral Implantology were screened clinically for the presence of DH and were included in the study based on the inclusion and exclusion criteria. The inclusion criteria of the study were: Subjects with a gingival index score of ≤2; Subjects who were medically/systemically fit and had no dental problems/active periodontitis apart from experiencing DH; Subjects with cervical abrasion, abfraction or gingival recession; Subjects of both genders of age 18-70 years; Non-lactating females; Non-smokers; Subjects who agreed to be compliant during the study. The exclusion criteria were: Subjects using any existing desensitizing therapy; Subjects with attrition; Medical (including psychiatric) and pharmacotherapeutic histories that may compromise the protocol and assessment of DH; Allergies and idiosyncratic responses to any of the product ingredients; Periodontal surgery in the preceding 3 months; Orthodontic appliance treatment within the previous 3 months; Teeth or supporting structures with any other painful pathology or defects; Teeth restored in the preceding 3 months and those with restorations extending into the test area; Abutment teeth for fixed or removable prostheses.

Sample Size:

The sample size estimation was undertaken using the G- power software. The effect size was 1.01, while the alpha error (%) was 5% and the power (%) was 95%. Hence the sample size calculated was 25 in each group.

Randomization:

The toothpastes concealed in plain white tubes were allocated randomly by a third person who was not involved in the study. The list of subjects and the group to which they belong was known only to the third person who kept a record within a computer data sheet. The allocation concealment was completed using case numbers assigned to each subject. The single, blinded, calibrated investigator performed all the clinical examination to avoid any

bias. The statistician was also blinded and was not aware of the allocation of the toothpastes to the individuals with the three groups.

Study Protocol:

The study was conducted on 75 subjects. The participants were categorized into following three groups:

Group-A: 25 subjects who were given a test toothpaste (5% Fluorocalcium phosphosilicate/Biomin-F®).

Group-B: 25 subjects who were given a comparative toothpaste (8% Arginine and calcium carbonate/ Pro-Argin®).

Group-C: 25 subjects who were given a placebo toothpaste.

The following clinical parameters were recorded at pre-baseline (day 1):

• Gingival Index (Loe and Sillness -1963)

• Plaque Index (Sillness and Loe-1964)

• Visual analog score (VAS) for evaluating DH using an air blast stimuli.

The Gingival Index and Plaque Index were assessed in the teeth having dentinal hypersensitivity. DH was also assessed by tactile examination by running a sharp explorer over the exposed buccal/ cervical region. An evaporative stimulus was applied using a 3 s blast of air from a dental unit syringe at 40–65 psi directed perpendicular and at a distance of 1–3mm to the exposed buccal cervical region. A VAS was scored only for the air blast stimuli using a scale from 0= no pain to 10=extreme pain. Subjects with a VAS score ≥ 5 were included in the study. Scaling and root planing was performed on each subject as well as oral hygiene instruction(s) with the demonstration of the modified bass technique of

toothbrushing was shown to each subject. At baseline 15 days after the pre-baseline all subjects were recalled for evaluation where all the parameters were reassessed. Following this evaluation the subjects were provided with a soft bristle toothbrush and the toothpastes were randomly allocated by a third person who was not a part of the study. After this appointment subjects were recalled after a 1 month interval at the post-baseline where all the parameters were reassessed. In this study, our primary outcome to be evaluated was reduction of DH whereas the secondary outcome was to evaluate changes with PI and GI.

Statistical Analysis:

The comparison of the three study groups with respect to the pre-baseline, baseline and post-baseline for PI, GI, and VAS scores was performed by Kruskal Wallis ANOVA, whereas pair wise comparisons were undertaken by Mann-Whitney U test. The percentage changes were evaluated by the Wilcoxon matched pairs test. The p value was kept as < 0.05.

Results:

The PI scores were found to be significant for Group A as compared to Group C. While a better reduction was found for Group A as compared to Group B and Group B as compared to Group C, but the differences were not statistically significant (Table-1/Figure-1). The GI scores were found to be significant for Group A as compared to Group C. Similar to the PI scores, the GI scores as well showed a better reduction for Group A as compared to Group B and Group B as compared to Group C, but the differences were not statistically significant (Table-2/Figure-2). The VAS scores were found to be significant for Group A as compared to Group B and Group C and for Group B as compared to Group C (Table-3/Figure-3).

Discussion:

In this study, Group-B was provided with a comparator Pro-Argin®formulation because several published studies[9-13] evaluating Pro-Argin® formulations comparing it with other available tubule occluding agents reported that Pro-Argin® toothpastes were superior to the other toothpastes. In this study, Group-A showed a better clinical reduction in DH than Group-B and Group-C and this difference was found to be statistically significant. The Group-B, however, also showed significant reduction of DH on an intragroup comparison and on comparision with Group-C.

An *invivo* study[6] comparing the 5% Fluorocalcium phosphosilicate toothpaste with 5% potassium nitrate, 10% strontium chloride, and a herbal formulation and reported that the 5% Fluorocalcium phosphosilicate toothpaste was more effective than the other toothpastes.[6] The authors indicated that the Biomin-F toothpaste contained a smaller particle size which reduced their abrasiveness and increased their penetration into the dentinal tubules and also reported that these particles could chemically bind to the tooth surface due to the presence of specific polymers which increased their retentiveness within the tubules.[6] An *in vitro* study[4] reported that the components within the 5% Fluorocalcium phosphosilicate dentifrice slowly dissolved to release calcium, phosphate and fluoride ions from a single composition which increased their bioavailability. These ions precipitate and crystallize to form FAP over the dentin surface and within the dentinal tubules that provide a deep occlusion within the tubules.[4] Also the fluoride was present within the glass instead of as a soluble additive hence more FAP formation was obtained and no undesirable fluorite was formed.[4] Another *in vitro* study[5] reported that FAP has a fluoride ion (F^-) which fits in the center of the triangle formed by the calcium ion (Ca^{+2}) in the apatite lattice. This stoichiometry provides the structure with more stability and a higher bond strength hence making it more acid resistant. The HCA crystal has the hydroxyl ion that is displaced above the Ca+2 triangle which distorts the

crystals and decreases the bond strength making it less resistant to an acid challenge.[5] Also one more *in vitro* study[14] demonstrated that the higher phosphate content helped in the rapid degradation of the glass lattice and increased the pH causing a rapid precipitation of ions forming FAP at a higher rate and occluding the dentinal tubules. The FAP formed rapidly and tubule occlusion was obtained as early as 6 hrs in comparison to the other toothpastes with soluble fluorides which took 7 days to occlude dentinal tubules.[14] These reasons may explain the superior efficacy of a 5% Fluorocalcium phosphosilicate toothpaste demonstrated in this randomized clinical trial.

Group-B were allocated the Pro-Argin® formulation containing toothpaste. A study comparing a Pro-Argin® formulation to a toothpaste containing 2% potassium ion and reported that the Pro-Argin® formulation was more effective.[11] Another study comparing a Pro-Argin® formulation with an 8% strontium acetate toothpaste and reported that the Pro-Argin® toothpaste to be more effective.[12] An *invivo* study[9] compared a Pro-Argin® formulation with a Novamin® formulation and Hydroxyapatite nanoparticles and observed that the Pro-Argin was superior to the Novamin® formulation but not to the hydroxyapatite nanoparticle formulation.[9] The Arginine (positively charged) and calcium carbonate from the desensitizing paste containing the Pro-Argin formulation in contact with the saliva binds to the negatively charged dentin to deposit Arginine calcium bicarbonate which is a dentin like mineral. This layer occludes the tubules up to 2 microns and has been reported to provide relief from DH.[3,13] Other reported studies[10,13] on acid erosion of the mineral layer formed by Pro-Argin® formulations have indicated that the layer was resistant to normal pulpal pressures and partially to an acid challenge. Therefore as evidenced in the present study the Pro-Argin® formulation showed a significant reduction of DH from prebaseline to postbaseline compared with Group-C.

The secondary objective of this study was to assess the effects of Biomin-F® on GI and PI. An *in vitro* study,[15] where it was observed that a F^- containing Bioactive Glass (BAG's) had an antimicrobial effects on several periodontal pathogens.[15] Therefore in the present study we evaluated the effects of the test and control toothpastes on both GI and PI. Our results showed that only Group-A (Biomin-F) showed a significant reduction of GI and PI at post-baseline.One plausible mechanism that may explain this finding would be that the F^- ion in the BAG initiates disruption in some of the periodontal pathogens. Furthermore, the pH elevation caused by the BAG sodium release is generally unfavourable for most bacteria and the increased osmotic pressure from ion dissolution, creates an environment where the bacteria cannot grow.[15] This causes a reduction in the bacterial load and its accumulation and may therefore be the reason that there was an observed clinical reduction in the PI scores. The reduction in the bacterial load and accumulation may also cause a reduction in inflammation thereby decreasing the GI scores and as such may explain why Group-A in particular showed a significant reduction of both the PI and GI scores at the postbaseline timepoint.

This study, however, is not without limitations. The main limitation of this study was that the long term efficacy of the test toothpaste was not evaluated. Furthermore, the results of this study cannot be generalized as non random sampling was undertaken. Although the results from the present study would indicate some short term benefit from using a Biomin-F ® toothpaste it would be appropriate to conduct further long term randomized clinical trials ($\geq$ 6 weeks) to determine whether this novel toothpaste may be an effective tubular occluding agent for the treatment of DH.

Conclusion:

In conclusion, all three groups showed a reduction in DH, however, only Group-A (5% Fluorocalcium phosphosilicate) showed a maximal reduction in DH and appeared within the limitations of the study to be more efficacious than both the comparator and placebo toothpastes in managing DH. Also the 5% Fluorocalcium phosphosilicate toothpaste showed a reduction in both the PI and GI scores as compared to the other two groups at postbaseline which may be as a result of its anti-bacterial and anti-inflammatory activity. Further clincal trials, however, are warranted in this direction to evaluate the efficacy of this novel toothpaste against other established comparator toothpastes.

References:

1. Addy M. *Introduction and Overview: Statement of the Problem. In: Gillam DG, Dentine Hypersensitivity – Advances in diagnosis, management and treatment*. London: Springer international publication; 2015: 1-11.
2. Holland GR, Narhi MN, Addy M, Gangarosa L, Orchardson R. Guidelines for the design and conduct of clinical trials on dentine hypersensitivity. *J Clin Periodontol* 1997; 24: 808-813.
3. Cummins D. Dentin hypersensitivity: From diagnosis to a breakthrough therapy for everyday sensitivity relief. *J Clin Dent* 2009; 20(1): 1-9.
4. Lynch E, Brauer DS, Karpukhina N, Gillam DG, Hill RG. Multi-component bioactive glasses of varying fluoride content for treating dentin hypersensitivity. *Dent Mater* 2012; 28(2): 168-178.
5. Brauer DS, Karpukhina N, O'Donnell MD, Law RV, Hill RG. Fluoride-containing bioactive glasses: effect of glass design and structure on degradation, pH and apatite formation in simulated body fluid. *Acta Biomater* 2010; 6(8): 3275-3282.

6. Gautam V, Halwai HK. Comparison of Clinical Efficacy of Four Dentifrices in the Management of Dentinal Hypersensitivity. *IJSR* 2017; 6(2): 339-340.
7. Da Cruz LPD, Hill RG, Chen X, Gillam DG. Dentine Tubule Occlusion by Novel Bioactive Glass-Based Toothpastes. *International Journal of Dentistry 2018*; 10.
8. Shaikh K, Pereira R, Gillam DG, Phad S. Comparative Evaluation of Desensitizing Dentifrices containing BioMin®, Novamin® and Fluoride on Dentinal Tubule Occlusion before and after a Citric Acid Challenge– A scanning Electron Microscope in-vitro Study. *J Odontol* 2018; 2:105.
9. Jena A, Shashirekha G. Comparison of efficacy of three different desensitizing agents for in-office relief of dentin hypersensitivity: A 4 weeks clinical study. *J Conserv Dent* 2015; 18(5): 389–393.
10. Kleinberg I. Sensitstat. A new saliva-based composition for simple and effective treatment of dentinal hypersensitivity. *Dent Today* 2002; 21: 42-47.
11. Nathoo S, Delgado E, Zhang YP, DeVizio W, Cummins D, Mateo LR. Comparing the efficacy in providing instant relief of dentin hypersensitivity of a new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride relative to a benchmark desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and to a control toothpaste with 1450 ppm fluoride: a three-day clinical study in New Jersey, USA. *J Clin Dent* 2009; 20(4): 123-130.
12. Patel R, Chopra S, Vandeven M, Cummins D. Comparison of the effects on dentin permeability of two commercially available sensitivity relief dentifrices. *J Clin Dent* 2011; 22(4): 108-112.
13. Petrou I, Heu R, Stranick M, Lavender S, Zaidel L, Cummins D et.al. A breakthrough therapy for dentin hypersensitivity: How dental products containing

8% arginine and calcium carbonate work to deliver effective relief of sensitive teeth. *J Clin Dent* 2009; 20(1): 23-31.

14. Mneimne M, Hill RG, Bushby AJ, Brauer DS. High phosphate content significantly increases apatite formation of fluoride-containing bioactive glasses. *Acta Biomater* 2011; 7(4): 1827-1834.
15. Liu J, Rawlinson SC, Hill RG, Fortune F. Strontium-substituted bioactive glasses in vitro osteogenic and antibacterial effects. *Dent Mater* 2016; 32(3): 412-422.

Table-1: Comparison of the three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline PI scores by Kruskal Wallis ANOVA

Groups	Pre-baseline		Baseline		Post-baseline	
	Mean	SD	Mean	SD	Mean	SD
Group A	1.52	0.25	1.54	0.26	0.59	0.21
Group B	1.53	0.28	1.55	0.27	0.62	0.22
Group C	1.51	0.33	1.54	0.33	0.72	0.30
H-value	0.1200		0.1290		3.6280	
p-value	0.9420		0.9370		0.1630	
Pair wise comparisons by Mann-Whitney U test						
Group A vs Group B	p=0.9227		p=0.9227		p=0.6071	
Group A vs Group C	p=0.7710		p=0.7785		p=0.0407*	
Group B vs Group C	p=0.7415		p=0.6766		p=0.1094	

Table-2: Comparison of the three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline GI scores by Kruskal Wallis ANOVA

Groups	Pre-baseline		Baseline		Post-baseline	
	Mean	SD	Mean	SD	Mean	SD
Group A	1.76	0.27	1.77	0.26	0.63	0.19
Group B	1.66	0.31	1.67	0.31	0.69	0.27
Group C	1.64	0.36	1.65	0.36	0.75	0.16
H-value	1.5980		1.6860		6.1360	
p-value	0.4500		0.4300		0.0470*	
Pair wise comparisons by Mann-Whitney U test						
Group A vs Group B	p=0.2483		p=0.2366		p=0.3320	
Group A vs Group C	p=0.3773		p=0.3879		p=0.0110*	
Group B vs Group C	p=0.9768		p=0.9613		p=0.4151	

Table-3: Comparison of the three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline VAS scores by Kruskal Wallis ANOVA

Groups	Pre-baseline		Baseline		Post-baseline	
	Mean	SD	Mean	SD	Mean	SD
Group A	5.58	0.65	5.58	0.65	0.51	0.46
Group B	5.42	1.04	5.42	1.04	2.36	0.97
Group C	5.25	0.70	5.25	0.70	4.02	0.83
H-value	5.1280		5.1280		56.0480	
p-value	0.0770		0.0770		0.0001*	
Pair wise comparisons by Mann-Whitney U test						
Group A vs Group B	p=0.0842		p=0.0842		p=0.0001*	
Group A vs Group C	p=0.0489*		p=0.0489*		p=0.0001*	
Group B vs Group C	p=0.6766		p=0.6766		p=0.0001*	

Figure Legends:

Figure-1: Comparison of three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline Plaque Index scores

Figure-2: Comparison of three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline Gingival Index scores

Figure-3: Comparison of three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline Visual Analog Scale scores

Figure-1: Comparison of three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline Plaque Index scores

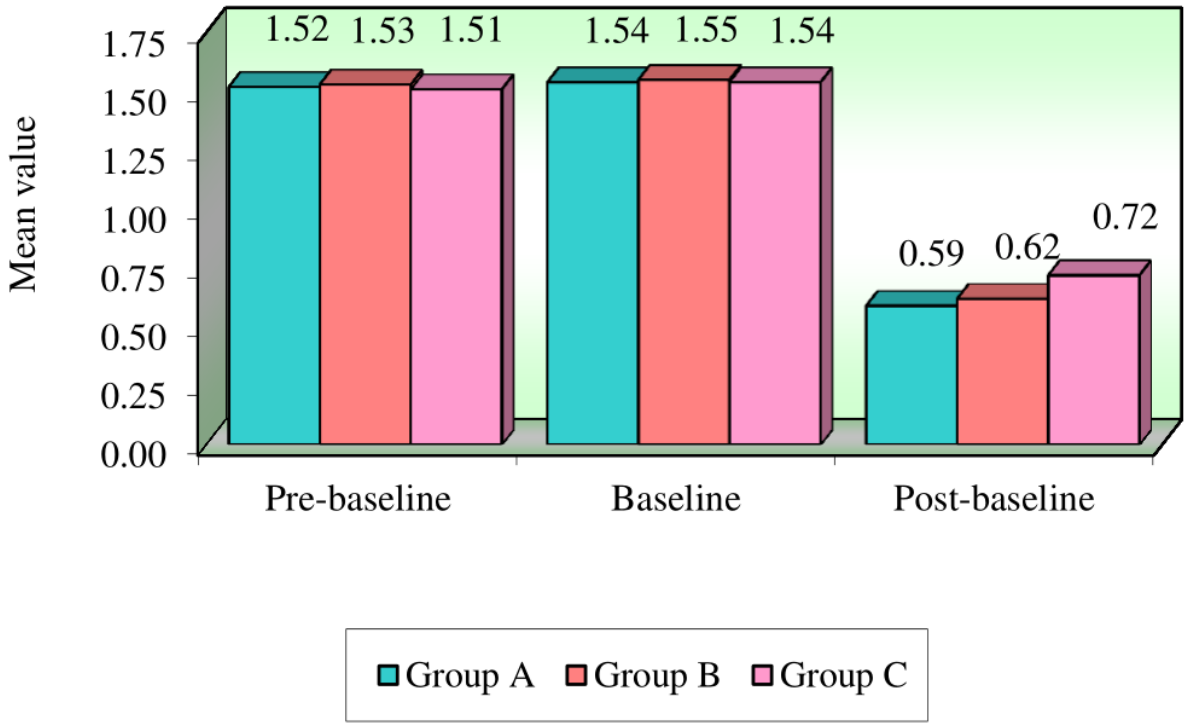

Figure-2: Comparison of three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline Gingival Index scores

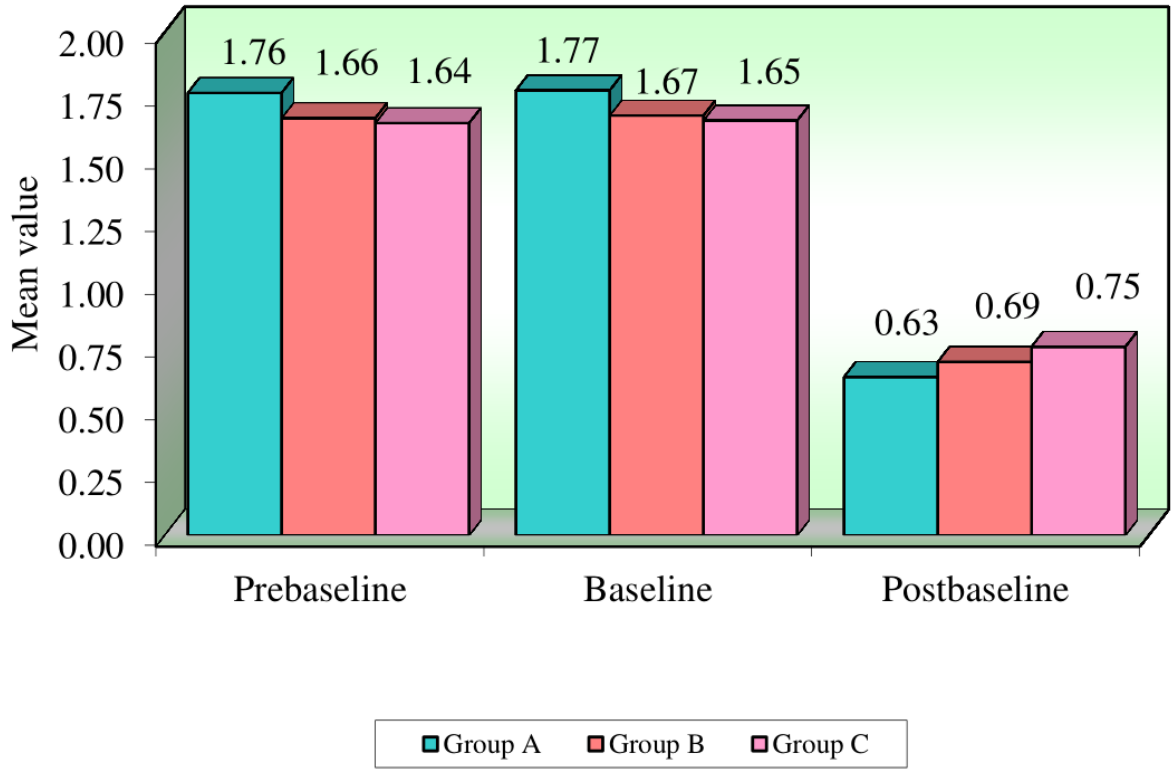

Figure-3: Comparison of three study groups (A, B, C) with respect to pre-baseline, baseline and post-baseline Visual Analog Scale scores